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PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Penetrating Agents

I, FRIEDRICH MEYER, of Schönenfelder Strasse 20, Hamburg-Wilhelmsburg, Germany, a German Citizen, do hereby declare the invention for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to an ointment, liniment, lotion or like preparation for topical application.

A few decades ago, it was still widely believed that the outer skin of warm-blooded animals was completely impervious from the outside. Although it is now known that the skin does not provide absolutely complete protection against chemical influences—there are cases recorded in toxicology of medicinal poisoning caused by salicylic-acid-containing ointments and of industrial poisoning caused by alkyl phosphates and other contact insecticides—the skin is fairly impervious, and so only very small quantities are really absorbed when ointments, powders, jellies and liniments are applied externally in the conventional manner. The cosmetic, pharmaceutical or other active agents contained in such preparations permeate the epidermis, as a rule, either not at all or so slowly that there is almost no chance of being sure that there is any action in the deep layers of the skin (including the corium and subcutis). By far the majority of the quantity applied penetrates merely very superficially into the so-called pores—which are definitely not entrances—to be perhaps emulsified or subsequently removed by rubbing or washing. Reliable penetration of the epidermis (absorption into the skin) or percutaneous resorption into the general circulation (absorption through the skin), however, are exceptional, and the quantities concerned are small. Notwithstanding contrary statements, proof is seldom available of definite penetration or resorption. The ratio of the quantity resorbed to the quantity applied is usually worse than 1:1000.

Since penetration of the epidermis occurs therefore either not at all or very slowly, many endeavours have been made to prolong the duration of the effect for days or even weeks. Most of the endeavours in this direction have been unsuccessful. Many appliances disclosed for this purpose do nothing more than retain the externally applied preparation at the place of action for as long as possible. This fact alone, however, shows that the rate of penetration or of resorption is very low. Detailed experiments by the Applicant have shown that the rate of resorption of the ordinary contents of ointments, jellies, liniments and other liquid or semi-solid preparations of active agents is very low if, indeed, it can be detected at all. Many hours or days pass before measurable quantities of active principle are absorbed.

The substances stated as vehicles, for instance, glycols, glycerin, ethanol or the like, are almost exclusively solvents or aids to solution. They have no effect either way on penetration and resorption. If an active agent can be percutaneously resorbed on its own, as can, for instance, some hormones, salicyclic acid and some nicotinic acid esters, the penetration or resorption may be adequate provided that the duration of the action can be of the order of days. However, it is exceptional for such a long time to be available. Most cosmetic, pharmaceutical and other active agents cannot be resorbed percutaneously, at least not in practice, and cannot therefore on their own penetrate the epidermis.

According to the present invention there is provided an ointment, liniment, lotion or like preparation for topical application, comprising an active agent which is to penetrate the epidermis, and, as an aid for assisting penetration of said active agent into the epidermis, a monovalent saturated or unsaturated aliphatic,

cycloaliphatic or aromatic alcohol having from 4 to 12 carbon atoms; an aliphatic, cycloaliphatic or aromatic hydrocarbon having from 5 to 12 carbon atoms; a terpene having from 9 to 15 carbon atoms; an aliphatic, cycloaliphatic or aromatic aldehyde, ketone or ester having from 4 to 10 carbon atoms: an essential oil or a substance containing an essential oil; a halogenated or nitrated aliphatic, cycloaliphatic or aromatic hydrocarbon having from 2 to 8 carbon atoms; or a mixture of two or more of such penetration aids, and any inert carrier necessary for forming said preparation, the carrier being such or being present in an amount such as not to prevent penetration by said penetration aid.

The use of the aforesaid penetrating aids in such a preparation for topical application enables active agents to be introduced readily and rapidly into deep layers of the skin and, if required, enables active agents to be resorbed through the skin. The procedure to be described hereinafter therefore enables:

(a) active agents, not resorbable on their own, to be absorbed percutaneously, and

(b) the percutaneous absorption of difficultly or slowly resorbable active agents to be speeded up considerably.

The advantages of this are that:

1. The required duration of the action is only a matter of minutes.

2. The relatively deep layers of the skin are reached rapidly and reliably, and

3. the rate of penetration can be varied within wide limits and can therefore be readily adapted to suit particular requirements.

The present preparation for topical application is therefore based on using certain vehicle substances and resides in that, in addition to known aids to solution which are often wrongly called aids to resorption, and which may form at least part of the inert carrier, vehicle substances are used which produce or assist penetration of the epidermis or resorption by the skin. Aids to penetration and resorption are therefore used in addition to aids to solution. The dwell time of the active agents in the skin can be controlled within wide limits by an appropriate choice of penetrating aids or by mixing with an aid to solution which has no effect on resorption. If, as is not so common, the active agent is sufficiently soluble in the penetrating aid, there is, of course, no need to use a special aid to solution. The present preparations containing the active agents dissolved in them are applied conventionally by being rubbed or massaged in or just by contact; in the case of liquid, an impregnated cotton wool pad with or without a cover can be used.

Conventional solvents, such as glycols, glycerin, ethanol or water, can usually be used.

The following compounds are very suitable as penetrating aids:

1. Monovalent, saturated and unsaturated aliphatic cycloaliphatic and aromatic alcohols having a total of from 4 to 12 carbon atoms, for instance, hexanol, hexenol, cyclohexanol and benzyl alcohol (N.B.—*monovalent*, secondary, tertiary and polyvalent alcohols are aids to solution rather than penetrating agents);

2. Aliphatic, cycloaliphatic and aromatic hydrocarbons having from 5 to 12 carbon atoms, for instance, hexane, hexene, cyclohexane and isopropylbenzene;

3. Terpenes having from 9 to 15 carbon atoms, for instance, thymene and 1-pinene;

4. Aliphatic, cycloaliphatic and aromatic aldehydes and ketones having from 4 to 10 carbon atoms, for instance, heptylaldehyde, cyclohexanone and benzaldehyde;

5. Aliphatic cycloaliphatic and aromatic esters having from 4 to 10 carbon atoms, for instance, isoamylacetate and benzylpropionate;

6. Essential oils or substances containing them, for instance, Ol. eucalypti, Ol. Rutae, cumin oil, limonene, thymol, fenchone and carbone;

7. Halogenated or nitrated aliphatic, cycloaliphatic and aromatic hydrocarbons having 2 to 8 carbon atoms, for instance, hexylbromide, hexylchloride, cyclohexylchloride, benzylchloride, o-dichlorobenzene and nitrocyclohexane; and

8. Mixtures or solutions of all these compounds.

It is to be noted that some of the chlorinated hydrocarbons included under (7) above are toxic or are skin irritants and care should be employed in using them, although they may be of use where an irritant action on the skin is required.

It is to be appreciated that the penetrating effect of the penetrating aids mentioned above is not equal and varies considerably from those which have a strong penetrating effect to those which have a weak penetrating effect, that is to say they require very long periods of contact with the skin to effect penetration.

The active agent of the present preparation for topical application may be a cosmetic agent, a pharmaceutical agent, such as tetracycline, or a dye, or pigment or any other agent which it is desired to introduce into the epidermis. In preparing the preparation, the active agent and penetrating agent are selected preferably so that the active agent is soluble in the penetrating agent, and such that the solution of active agent and penetrating agent is stable. If desired, or if the active agent is not readily soluble in the penetrating agent, a solvent aid may be added which may form part of the carrier.

If it is desired to prepare a non-liquid preparation, such as an ointment, then the above solution can be turned into a jelly or unguent by known pharmaceutical techniques such as by adding a thickner, e.g. fumed silica, or an unguent base, However, it must be borne in

mind that thickners or unguent bases may reduce the penetration rate, although this may not be of disadvantage if the penetrating aid has such a high rate of penetration that it is desirable to control the rate of penetration.

In general, fatty unguent bases should be avoided as they have an inhibiting effect on the penetrating aid, although, as indicated, they may be useful in controlling the rate of penetration. Thus, it is preferred not to use unguent bases such as liquid paraffin, solid paraffin, petroleum jelly, olive oil, glycerine, *Adeps lanae anhydrous*, lanolin, *Adeps suillus*, stearyl alcohol, cetyl alcohol and zinc ointment bases.

The invention will now be illustrated by the following Examples.

EXAMPLE 1

Malachite green, which is very easy to recognise in the skin as a pigment and which therefore permits of ready histological identification in a frozen section, has strong fungicidal properties ("active principle"). Malachite green dissolved in ethyl glycol does not penetrate the epidermis, but when cyclohexane is used as a penetrating agent in addition to malachite green, which is an aid to solution, malachite green can definitely be detected in deep layers of the skin (corium) after a few minutes. The rate of penetration increases rapidly as the proportion of cyclohexane increases.

EXAMPLE 2

A fluorescing pigment, Rhodamine B, acting as a model for any active principle, is not absorbed from an ethanolic or aqueous solution nor after solution in ethyl glycol, propylene glycol or glycerin. When a penetrating agent is added to these aids to solution, a deep penetration results from a short contact. For instance, if as little as 10% of cyclohexane is added to a Rhodamine B solution in ethyl glycol, the pigment is visible in deep layers of the skin after as little as thirty minutes later. When 50% of cyclohexane is added, Rhodamine is detected in the corium after as little as three minutes; after ten minutes it can be detected even in the subcutaneous fatty tissue.

However, if a mixture of cyclohexanone and Rhodamine B is applied, the Rhodamine B does not appear in the corium because it is not sufficiently soluble in cyclohexane.

EXAMPLE 3

The following Table lists the results obtained with various penetrating agents:

KEY TO TABLE

Column 1: Penetrating agent—substances tested as to their penetrating agent properties.
Column 2: L% = addition (in percentage by volume) of an aid to solution which has no effect on penetrating properties. Usually ethylglycol (see page 2 of table).
50 = 50% of aid to solution.
– = without any addition.
Column 3: Active principle:
Ma = malachite green
Rh = Rhodamine B
Or = Orcein
Mb = Methylene blue
Su = Sudan III
Ac = Acridine orange
Na = Sodium fluoroescein
Fl = Fluorescein
Eo = Eosin
Ha = Harmine
Fu = Fuchsine
Er = Erythrosine
Sa = Safranine
To = Toluidine blue
Ge = Gentian violet.
Column 4: t = duration of action in minutes (') or hours (h).
Column: Epithelium
Column 6: Hair follicles
Column 7: Corium
Column 8: Subcutis

HISTOLOGICAL FINDINGS

\+ strong colouring or fluorescence
(+) noticeable colouring or fluorescence
= slight colouring or fluorescence
– no colouring or fluorescence

There is genuine penetration only when the active principle can be detected in the corium (column 7 or in the subcutis (column 8).
Column 9: Remarks.

The findings were made on guinea pigs unless other wise specified in column 9.

Penetrating Agent	L %	Active substance	t	Epith-elium	Hair shafts	Corium	Sub-cutis	Remarks
1	2	3	4	5	6	7	8	9
Methanol	—	Ma	2h	+	—	—	—	
Ethanol	—	Ma	2h	=	—	—	—	
Ethanol	—	Ma	24h	=	—	—	—	
Ethanol	—	Rh	3 h	=	—	—	—	
n-Propanol	—	Ma	2h	—	—	—	—	
i-Propanol	—	Ma	2h	—	—	—	—	
n-Butanol	50	Ma	2h	=	=	—	—	
n-Butanol	50	Ma	20h	=	(+)	=	—	
i-Butanol	50	Ma	2h	=	=	—	—	
tert. Butanol	50	Ma	2h	=	—	—	—	
n-Pentanol	50	Ma	2h	(+)	(+)	=	—	
i-Amylalcohol	50	Ma	2h	(+)	(+)	=	—	
3-Pentanol	50	Ma	2h	(+)	(+)	=	—	
n. prim. Hexanol	50	Ma	2h	+	+	+	=	
„	—	Rh	2h	+	+	+	+	
„	—	Rh	5′	=	=	—	—	Cat
„	—	Rh	30′	(+)	(+)	=	—	Cat
„	—	Rh	2h	+	+	(+)	=	Rabbit
„	—	Rh	30′	(+)	(+)	(+)	=	
n-Heptanol	50	Ma	2h	+	+	+	(+)	
prim. Octanol	50	Ma	2h	+	+	(+)	=	
sec. Octanol	50	Ma	2h	(+)	(+)	=	—	
Nonylalcohol	50	Ma	2h	+	+	+	+	
Decylalcohol	50	Ma	2h	+	+	+	+	
Dodecylalcohol	50	Ma	2h	+	+	+	=	
n. prim.	50	Rh	2h	+	+	+	+	
Hexene(3)ol(1)	50	Rh	2h	+	(+)	(+)	=	
Heptene(3)ol(1)	50	Rh	2h	+	(+)	=	=	
Cyclohexanol	50	Rh	2h	(+)	(+)	=	—	
Benzylalcohol	50	Rh	2h	(+)	(+)	=	—	

1	2	3	4	5	6	7	8	9
Phenylmethyl-alcohol	50	Rh	2h	—	—	—	—	
Phenylethyl-alcohol	50	Rh	2h	—	—	—	—	
Methylglycol	50	Rh	2h	=	—	—	—	
Methylglycol	—	Rh	2h	=	—	—	—	
Ethylglycol	—	Ma	2h	=	—	—	—	
»	—	Ma	20h	=	=	—	—	
»	—	Rh	2h	=	—	—	—	see Example 2
»	—	Rh	2h	=	—	—	—	Dog
»	—	Rh	2h	=	—	—	—	Rabbit
»	—	Rh	2h	—	—	—	—	Cat
»	—	Mb	2h	—	—	—	—	
»	—	Mb	6h	—	—	—	—	
»	—	Or	2h	=	=	—	—	
Ethyleneglycol	—	Rh	2h	—	—	—	—	
1,2-propylene glycol	—	Rh	2h	=	—	—	—	
1,3-butyleneglycol	—	Rh	2h	=	—	—	—	
Carbitol	—	Rh	2h	=	=	—	—	
Hexamethylene glycol	50	Rh	2h	=	—	—	—	
Glycerin	50	Rh	2h	=	=	—	—	
Geraniol	50	Rh	2h	—	—	—	—	
Linaloöl	50	Rh	2h	—	—	—	—	
Terpinol hydrate	90	Rh	2h	—	—	—	—	
Terpineol, thickly viscous	50	Rh	2h	(+)	(+)	=	—	
Terpineol, fresh	50	Rh	2h	+	(+)	(+)	—	
Menthol	50	Rh	2h	=	=	=	—	
Eucalyptol	50	Rh	2h	+	+	(+)	=	
Cumin alcohol	50	Rh	2h	=	=	—	—	
Anethole	50	Rh	2h	—	—	—	—	
Eugenol	50	Rh	2h	—	—	—	—	
Isoeugenol	50	Rh	2h	—	—	—	—	

1	2	3	4	5	6	7	8	9
Isoeugenol	—	Rh	2h	−	−	−	−	
Carvacrol	50	Rh	2h	−	−	−	−	
Apiole	50	Rh	2h	−	−	−	−	
Safrol	50	Rh	2h	=	=	−	−	
Tinct. Aloes	—	Rh	2h	=	−	−	−	
„ Colocynthid.	—	Rh	2h	=	−	−	−	
„ Cantharidis	—	Rh	2h	=	−	−	−	
„ Capsioi	—	Rh	2h	=	−	−	−	
Spirit. Sinapis	—	Rh	2h	=	−	−	−	
Pentane	50	Rh	2h	+	+	+	+	
Hexane	50	Rh	2h	+	+	+	+	
Heptane	50	Rh	2h	+	+	+	+	
Pentene (2)	50	Rh	2h	+	+	+	+	
Hexene (1)	50	Rh	2h	+	+	+	=	
Heptene (1)	50	Rh	2h	+	+	+	+	
Octene (1)	50	Rh	2h	+	+	+	+	
Nonene (1)	50	Rh	2h	+	+	+	+	
Decene (1)	50	Rh	2h	+	+	+	+	
Cyclohexane	—	Rh	10′	=	=	=	=	
„	—	Rh	30′	=	(+)	=	=	
„	—	Or	30′	=	−	−	−	
„	—	Or	3h	=	=	−	−	
„	—	Mb	2h	=	=	−	−	
„	—	Mb	h	=	=	−	−	
„	20	Or	2h	(+)	+	=	=	
„	25	Rh	10′	+	+	+	+	
„	25	Rh	30′	+	+	+	+	
„	25	Or	30′	+	+	=	=	
„	25	Or	1h	+	+	+	+	
„	25	Mb	2h	=	=	=	−	
„	25	Ma	1h	=	(+)	=	−	

1	2	3	4	5	6	7	8	9
Cyclohexane	25	Rh	30′	+	+	(+)	=	Dog
,,	25	Rh	30′	+	+	=	=	Cat
,,	25	Rh	60′	+	+	+	+	Cat
,,	40	Ma	1h	+	(+)	=	−	
,,	50	Ma	1h	+	+	+	=	
,,	50	Ma	2h	+	+	=	=	
,,	50	Su	2h	+	+	=	=	
,,	50	Or	1h	+	+	+	=	
,,	50	Ac	30′	+	+	(+)	=	
,,	50	Ac	1h	+	+	(+)	=	
,,	50	Na	30′	+	+	(+)	=	
,,	50	Na	1h	+	+	+	=	
,,	50	Fl	30′	(+)	=	−	−	
,,	50	Fl	1h	(+)	=	(+)	=	
,,	50	Eo	1h	+	+	+	+	
,,	50	Rh	2h	=	=	=	−	
,,	50	Rh	5′	+	+	(+)	(+)	
,,	50	Rh	10′	+	+	+	+	
,,	50	Rh	30′	+	+	+	+	
,,	50	Rh	1h	+	+	+	+	
,,	50	Rh	30′	+	+	=	=	Dog
,,	50	Rh	1h	+	+	+	+	Dog
,,	50	Rh	30′	+	+	=	=	Cat
,,	50	Rh	10′	(+)	(+)	(+)	(+)	Rabbit
,,	50	Rh	30′	+	+	+	+	Rabbit
,,	50	Rh	90′	+	+	+	+	Rabbit
,,	50	Ha	30′	+	+	(+)	=	Dog
,,	50	Ha	30′	+	+	(+)	(+)	
,,	50	Ha	10′	=	=	−	−	
,,	75	Ma	1h	+	+	+	=	
,,	75	Ma	2h	+	+	(+)	(+)	

1	2	3	4	5	6	7	8	9
Cyclohexane	75	Fu	2h	+	+	(+)	(+)	
„	75	Er	2h	+	+	(+)	(+)	
„	75	Sa	2h	+	+	(+)	=	
„	75	Ge	2h	+	+	(+)	−	
„	75	To	2h	+	+	=	=	
„	75	Or	30′	+	+	(+)	=	
„	75	Or	3h	+	+	+	(+)	
„	75	Rh	2′	(+)	(+)	=	−	
„	75	Rh	5′	+	(+)	(+)	=	
„	75	Rh	10′	(+)	(+)	(+)	(+)	
„	75	Rh	30′	+	+	+	+	
„	75	Rh	2h	+	+	+	+	
„	75	Rh	30′	+	+	=	=	Dog
„	75	Rh	30′	+	+	=		Cat
„	80	Or	1h	(+)	+	(+)	−	
„	80	Rh	1h	+	+	+	=	
„	90	Rh	1h	+	+	(+)	=	
Methyl-cyclohexane	50	Rh	2h	+	+	+	+	
Benzene	50	Rh	2h	+	+	+	=	
Toluene	50	Rh	2h	+	+	+	(+)	
Paracymene	50	Rh	2h	+	+	+	=	
Cumene	50	Rh	2h	+	+	(+)	=	
Limonene	50	Rh	1h	(+)	(+)	=	−	
1,2-diethoxy-ethene	50	Rh	2h	(+)	=	−	−	
1,2-dibutoxy-ethene	50	Rh	2h	+	+	+	+	
Hexalkoxy-ethane	50	Rh	2h	−	−	−	−	
Dimethoxy-ethane	50	Rh	2h	(+)	=	−	−	
Oleum Rutae	50	Rh	1h	+	+	(+)	(+)	
Cumin oil	50	Rh	1h	+	+	(+)	(+)	
Ol.Menth.	50	Rh	1h	+	+	(+)	(+)	

1	2	3	4	5	6	7	8	9
Ol.Eucalypti	50	Rh	1h	+	+	(+)	(+)	
Ol.Galangae	50	Rh	1h	+	(+)	=	=	
Ol.Tanaceti	50	Rh	1h	(+)	(+)	=	=	
Peppermint oil	50	Rh	1h	(+)	(+)	(+)	–	
Ol.Camphoric	50	Rh	1h	(+)	(+)	=	=	
Ol.Sabinae	50	Rh	1h	=	=	=	=	
Ol.Pini sibin	50	Rh	1h	=	=	=	–	
Ol.Menth.pip.	50	Rh	1h	(+)	=	=	–	
Ol.Terebinth.	50	Rh	1h	(+)	(+)	=	–	
„	50	Rh	2h	+	+	+	(+)	
Ol.Juniperi	50	Rh	1h	=	=	=	–	
Ol.Petrosel.	50	Rh	1h	=	=	–	–	
Ol.Thymi	50	Rh	1h	=	=	–	–	
Ol.Balsami Copaivae	50	Rh	1h	=	=	–	–	
Sassafras oil.	50	Rh	2h	(+)	(+)	–	–	
Ol. Anisi	50	Rh	1h	–	–	–	–	
Peru balsam	50	Rh	1h	–	–	–	–	
Ol.Calami	50	Rh	1h	–	–	–	–	
Patchiouli oil	50	Rh	1h	–	–	–	–	
Ol.Pagi ethen.	50	Rh	1h	–	–	–	–	
Tolu oil.	50	Rh	1h	–	–	–	–	
Ol. Pimentae	50	Rh	1h	–	–	–	–	
Ol. Origani orotici	50	Rh	1h	–	–	–	–	
Ajowan oil.	50	Rh	1h	–	–	–	–	
Ol. Spicae	50	Rh	1h	–	–	–	–	
Thymene(1-Pinene)	50	Rh	1h	+	+	(+)	(+)	
α-Pinene	50	Rh	1h	(+)	+	(+)		
Propionaldehyde	50	Rh	1h	=	=	–	–	
Butylaldehyde	50	Rh	1h	=	=	–	–	
Hexylaldehyde	50	Rh	2h	=	=	=	–	

1	2	3	4	5	6	7	8	9
Heptylaldehyde	50	Rh	2h	=	=	=	=	
Octylaldehyde	50	Rh	2h	=	=	—	—	
Nonylaldehyde	50	Rh	2h	=	=	—	—	
n-capronaldehyde	50	Rh	2h	=	=	—	—	
Cyclohexanone	50	Rh	2h	=	=	=	—	
Butanone	50	Rh	2h	=	—	—	—	
Methylaceto-phenone	50	Rh	2h	=	=	—	—	
Methylheptyl-ketone	50	Rh	2h	=	=	=	—	
Methylnonyl-ketone	50	Rh	2h	(+)	(+)	=	—	
Citral	50	Rh	2h	=	=	—	—	
Citronellal	50	Rh	2h	=	—	—	—	
Pulegone	50	Rh	2h	(+)	(+)	=	=	
Thujone	50	Rh	2h	=	=	=	—	
Fenchone	50	Rh	2h	=	=	—	—	
Carvon	50	Rh	2h	=	=	=	—	
Cumaldehyde	50	Rh	2h	=	=	—	—	
Cinnemal	50	Rh	2h	=	—	—	—	
Acetone	50	Rh	2h	=	—	—	—	
Dioxane	50	Rh	2h	=	—	—	—	
Acetylacetate	50	Rh	2h	=	=	—	—	
i.amylacetate	50	Rh	2h	(+)	(+)	(+)	—	
n-octylacetate	50	Rh	2h	=	=	—	—	
Triacetate glycerol	50	Rh	2h	=	—	—	—	
Acetoacetic acid ethyl ester	50	Rh	2h	=	—	—	—	
Benzyl acetate	50	Rh	2h	=	=	=	—	
Benzyl propionate	50	Rh	2h	(+)	=	—	—	
Benzyl butyrate	50	Rh	2h	(+)	=	=	—	
Benzyl benzoate	50	Rh	2h	=	=	—	—	

1	2	3	4	5	6	7	8	9
Salicylic methyl acid ester	50	Rh	2h	=	=	—	—	
Salicylic amyl ester	50	Rh	2h	=	—	—	—	
Benzoic acid ethyl ester	50	Rh	2h	=	=	—	—	
Phenyl acetic acid methyl ester	50	Rh	2h	=	—	—	—	
Phenyl acetic acid ethyl ester	50	Rh	2h	=	—	—	—	
Phenylethyl-acetate	50	Rh	2h	=	=	—	—	
p-cresolmethyl ether	50	Rh	2h	=	=	=	—	
p-cresolethyl-ether	50	Rh	2h	=	=	=	—	
Diphenyl ether	50	Rh	2h	=	=	—	—	
Dimethyl phthalate	50	Rh	2h	=	—	—	—	
Menthyl-valerianate	50	Rh	2h	=	=	=	—	
Geranyl acetate	50	Rh	2h	=	=	—	—	
Geranyl formiate	50	Rh	2h	=	=	=	—	
Geranyl propionate	50	Rh	2h	=	=	=	—	
Geranyl butyrate	50	Rh	2h	=	=	—	—	
Linalyl acetate	50	Rh	2h	=	=	—	—	
Terpinyl acetate	50	Rh	2h	=	=	—	—	
Fenchyl acetate	50	Rh	2h	=	=	—	—	
Sabinol acetate	50	Rh	2h	=	=	—	—	
Bornyl acetate	50	Rh	2h	=	=	—	—	
Benzyl cinnamate	50	Rh	2h	=	—	—	—	
n-valeric acid diethyl amide	50	Rh	2h	=	—	—	—	
Dichloro-ethylene	50	Rh	2h	(+)	(+)	=	=	
Trichloroethylene	50	Rh	2h	(+)	(+)	=	=	
Tetrachloroethylene	50	Rh	2h	(+)	(+)	=	—	
n-allyl bromide	50	Rh	2h	+	+	+	+	
n-allyl chloride	50	Rh	2h	+	+	(+)	=	
Dibromo ethane	50	Rh	2h	+	+	(+)	(+)	
Dichloro ethane	50	Rh	2h	+	+	(+)	(+)	

1	2	3	4	5	6	7	8	9
Tetrachloro-ethane	50	Rh	2h	(+)	(+)	=	=	
Tetrabromo ethane	50	Rh	2h	(+)	(+)	=	−	
n-butyl bromide	50	Rh	2h	(+)	(+)	=	−	
n-amylbromide	50	Rh	2h	(+)	(+)	=	=	
sec. amyl bromide	50	Rh	2h	(+)	(+)	(+)	=	
n-hexyl bromide	50	Rh	2h	=	+	(+)	(+)	
n-heptyl bromide	50	Rh	2h	+	+	(+)	=	
n-octyl bromide	50	Rh	2h	(+)	(+)	=	=	
i-butylene bromide	50	Rh	2h	(+)	(+)	(+)	−	
Cyclohexyl chloride	50	Rh	2h	+	+	+	+	
n-dichloro benzene	50	Rh	2h	+	(+)	(+)	(+)	
Benzyl chloride	50	Rh	2h	=	=	=	−	
1-chloro-1,2-di-ethoxyethene	50	Rh	2h	+	+	+	+	
1,2-dichloro-1,2-diethoxy-ethene	50	Rh	2h	+	+	+	+	
Ethyl-chlorhydrin	50	Rh	2h	=	−	−	−	
Nitromethane	50	Rh	2h	=	−	−	−	
Nitroethane	50	Rh	2h	=	−	−	−	
1-nitropropane	50	Rh	2h	=	−	−	−	
2-nitropropane	50	Rh	2h	(+)	−	−	−	
Nitrocyclohexane	50	Rh	2h	+	+	+	(+)	
α-picoline	50	Rh	2h	−	−	−	−	
2,4-lutidine	50	Rh	2h	−	−	−	−	
Paraffinum liquid	50	Rh	2h	=	−	−	−	
Yellow paraffin jelly	50	Rh	2h	−	−	−	−	
Yellow paraffin oil	50	Rh	2h	−	−	−	−	
Oleum Olivarum	50	Rh	2h	=	−	−	−	
Ol. Arachidis.	50	Rh	2h	=	−	−	−	
Ol. Amygdalarum	50	Rh	2h	=	−	−	−	
Ol.Jecoris Aselli.	50	Rh	2h	=	−	−	−	

1	2	3	4	5	6	7	8	9
Unguent. molle DAB.	—	Rh	2h	=	=	—	—	
Ung. Paraffini	—	Rh	2h	=	=	—	—	
Ung. Glycerin	—	Rh	2h	(=)	=	—	—	
Adeps lanae	—	Rh	2h	=	=	—	—	
Lanolin	—	Rh	2h	(+)	=	—	—	
Tween 20	50	Rh	2h	=	—	—	—	
Tween 80	50	Rh	2h	=	—	—	—	
Squalene	50	Rh	2h	(+)	(+)	—	—	
»	50	Rh	1/2h	=	=	—	—	
Squalene-(Perhydrosqualene)	50	Rh	1/2h	=	=	—	—	
»	50	Rh	1h	(+)	(+)	—	—	
»	50	Rh	2h	+	(+)	=	=	
Comparison: Cyclohexane	50	Rh	10′	+	+	+	+	
Liniment to Federal German Patent Spec. 801,283	—	Rh	1h	=	(+)	—	—	
Liniment to Federal German Patent Spec. 870,323	—	Rh	1h	+	(+)	—	—	thickly viscous
»	—	Rh	1h	+	+	=	—	thinly viscous

EXAMPLE 4

0.5% by weight solution of tetracycline is prepared in a mixture of equal parts by weight of *n*-undecane and ethylene glycol. The resulting lotion is a liquid which can be resorbed through the skin to pass through the epidermis to reach the corium in as short a time as 30 minutes after external application.

EXAMPLE 5

50 mg./ml. of fumed silica are added to the preparation of Example 4 to result in a gelatinous ointment which is a semi-solid preparation and from which the tetracycline can be resorbed through the skin very rapidly.

EXAMPLE 6

Example 4 is repeated, replacing the ethylene glycol with *n*-docosane, stearyl alcohol or cetyl alcohol all of which have such a strong inhibiting effect on the penetration aid than no penetration of the teracycline in the corium could be detected.

EXAMPLE 7

A lotion was prepared comprising a 0.5% solution of tetracycline in a mixture consisting of 50% *n*-undecane, 35% ethylene glycol and 15% cetyl alcohol. After external application of this lotion, tetracycline could be detected in the corium, but the rate of penetration was much slower than with the preparation of Example 4.

WHAT I CLAIM IS:—

1). An ointment, liniment, lotion or like preparation for topical application, comprising an active agent which is to penetrate the epidermis, and, as an aid for assisting penetration of said active agent into the epidermis, a monovalent saturated or unsaturated aliphatic, cycloaliphatic or aromatic alcohol hav-

ing from 4 to 12 carbon atoms; an aliphatic, cycloaliphatic or aromatic hydrocarbon having from 5 to 12 carbon atoms; a terpene having from 9 to 15 carbon atoms; an aliphatic, cycloaliphatic or aromatic aldehyde, ketone or ester having from 4 to 10 carbon atoms; an essential oil or a substance containing an essential oil; a halogenated or nitrated aliphatic, cycloaliphatic or aromatic hydrocarbon having from 2 to 8 carbon atoms; or a mixture of two or more of such penetration aids, and any inert carrier necessary for forming said preparation, the carrier being such or being present in an amount such as not to prevent penetration by said penetration aid.

2). A preparation as claimed in Claim 1, wherein the preparation also includes a solvent for the active agent and/or penetration aid.

3). A preparation as claimed in Claim 1 or 2, wherein the penetration aid is one which normally has a high rate of penetration into the epidermis, and wherein there is present an inhibitor, which may form part of the carrier, for reducing the rate of penetration.

4). An ointment, liniment, lotion or like preparation for topical application in accordance with Claim 1 substantially as hereinbefore described in any one of Examples 1 to 5 and 7 of the foregoing Examples.

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